Complete Summary

GUIDELINE TITLE

The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in adults.

BIBLIOGRAPHIC SOURCE(S)

ASBMT Position Statement. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in adults. Biol Blood Marrow Transplant 2008 Feb;14(2):135-6. [2 references] PubMed

Oliansky DM, Appelbaum F, Cassileth PA, Keating A, Kerr J, Nieto Y, Stewart S, Stone RM, Tallman MS, McCarthy PL Jr, Hahn T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults: an evidence-based review. Biol Blood Marrow Transplant 2008 Feb;14(2):137-80. [144 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
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SCOPE

DISEASE/CONDITION(S)

Acute myeloid leukemia (AML)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Internal Medicine
Oncology
Pathology

INTENDED USERS

Health Plans
Managed Care Organizations
Patients
Physicians

GUIDELINE OBJECTIVE(S)

- To assemble and critically evaluate all the valid, peer-reviewed evidence regarding the role of cytotoxicÂ therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia (AML) in adults
- To make treatment recommendations based on the available evidence
- To identify discrepancies in study design or methodology among published studies that may impact on the quality of evidence
- To identify needed areas of additional research

TARGET POPULATION

Adult (≥15 years) patients with acute myelogenous leukemia (AML) who are candidates for hematopoietic stem cell transplantation

INTERVENTIONS AND PRACTICES CONSIDERED

1. Autologous stem cell transplantation (SCT)
2. Chemotherapy
3. Allogeneic SCT
4. Human leukocyte antigen (HLA) matched related donor allogeneic SCT
5. Peripheral blood stem cell transplantation (PBSCT)
6. Myeloablative conditioning regimens, including total body irradiation-containing regimens
7. Reduced-intensity conditioning regimensÂ

MAJOR OUTCOMES CONSIDERED

- Disease-free, event-free, relapse-free, leukemia-free, and overallÂ survival
- Treatment-related toxicity
- Time from first complete remission to first relapse or death

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

PubMed and Medline, the Web sites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were searched August 8, 2006, using the search terms ''acute myeloid leukemia'' or ''acute myelogenous leukemia'' and ''transplant,'' limited to human trials, English language, and a publication date of 1990 or later. An updated search was conducted in early May 2007, limited to August 9, 2006, to April 30, 2007. Manuscripts were excluded if they were published before 1990, included <50 acute myelogenous leukemia (AML) patients, were not peer reviewed, were editorials, letters to the editor, Phase I (dose-escalation or dose-finding) studies, reviews, consensus conference papers, practice guidelines, laboratory studies with no clinical correlates, did not focus on an aspect of therapy with hematopoietic stem cell transplantation (HSCT) for the treatment of adult AML, or if >50% of the study population was <15 years and the results were not stratified by age. In addition, for a manuscript to be included, a minimum of 70% of study subjects had to be AML patients, or study results had to be stratified by disease. Abstracts and presentations at national or international meetings were not included as evidence in this review because of their lack of peer review andÂ the limited availability of details on study design and results, and because they are usually presented as preliminary, not final, analyses of clinical trial data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case control or cohort studies; high-quality case control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal

2-	Case control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies (e.g., case reports, case series)
4	Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields of this summary define criteria used to grade the studies included in this review and to grade the treatment recommendations.

Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan also were considered in evaluating the studies. Several multicenter clinical trials were designed to biologically assign patients to a treatment arm based on the availability of a donor (''biologic allocation''). These studies of allogeneic (allo) HSCT versus chemotherapy are therefore graded as level ''2'' evidence, not level ''1,'' because they are not statistically randomized controlled trial designs. Autologous (auto) hematopoietic stem cell transplantation (HSCT) versus chemotherapy studies were graded as level ''1'' evidence if the study design included a statistically randomized controlled trial.

Clinical studies are described with enough detail to give a concise summary of study design, sample size, and eligibility criteria. All data in the text and tables were abstracted from the original manuscripts by the first author, then double checked for accuracy and clarity by 2 other authors and 1 additional reviewer. In some articles there were discrepancies within the data reported and, in these cases, the data most consistent with the text of the article were presented in this review. The last author takes responsibility if errors remain.Â

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The American Society for Blood and Marrow Transplantation (ASBMT), in 1999, began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of blood and marrow transplantation in the therapy of selected diseases. The steering committee that was convened to oversee the projects invited an independent panel of disease-specific experts to conduct each review.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (1++ to 4) and the grades of recommendation (A-D) are defined at the end of the "Major Recommendations" field.Â

The following guidelines are offered for the role of stem cell transplantation (SCT) as therapy for acute myeloid leukemia (AML) in adults, and are based on consensus reached by an expert panel following an evidence-based review of the literature:

Transplantation versus Chemotherapy

1. There is no significant advantage of autologous SCT over chemotherapy. Most of the data reflect outmoded treatment strategies, however, and studies using

modern technologies may affect outcomes. (**Grades of Recommendation A and B, Highest Level of Evidence 1+ and 1-**)

2. There is a survival advantage for allogeneic SCT vs. chemotherapy for patients under age 55 with high risk cytogenetics. (**Grade of Recommendation A, Highest Level of Evidence 1+**)
3. There is insufficient evidence to routinely recommend allogeneic SCT for patients with intermediate risk cytogenetics, although this is a reasonable strategy. (**Grade of Recommendation A, Highest Level of Evidence 1+**)
4. There is no survival advantage for allogeneic SCT in patients under age 55 with low risk cytogenetics. (**Grade of Recommendation A, Highest Level of Evidence 1+)**
5. There are insufficient data to make a recommendation for the use of myeloablative regimens for patients over age 55. (**Grade of Recommendation A, Highest Level of Evidence 1+**)
6. There are insufficient data to make a recommendation for reduced intensity conditioning (RIC) allogeneic SCT vs. chemotherapy. (**No Recommendation, Highest Level of Evidence 2**-)
7. For patients in second complete remission, allogeneic SCT is recommended if there is an available donor. Otherwise an autologous SCT is recommended. (**Grade of Recommendation D, Highest Level of Evidence 4**)

Transplantation Techniques

1. A human leukocyte antigen (HLA)-matched related donor allogeneic SCT is recommended over autologous SCT, if a matched-related donor is available. For matched unrelated donor allogeneic SCT, there are insufficient data to make a recommendation over autologous SCT. Available studies, however, do not reflect modern techniques in supportive care, stem cell source, or the use of molecular HLA typing. (**Grade of Recommendation B, Highest Level of Evidence 2++)**
2. Autologous peripheral blood stem cell transplant (PBSCT) is recommended over autologous bone marrow transplant (BMT) due to improvements in safety and early mortality. Long-term outcomes have not been studied prospectively, however, and the impact of autologous PBSCT on overall survival is not known. (**Grade of Recommendation C, Highest Level of Evidence 2+**)
3. There is no evidence of a survival advantage with purged BMT and insufficient data to make a recommendation for purging of PBSCT for autologous SCT. (**Grade of Recommendation C, Highest Level of Evidence 2+**)
4. There are insufficient data to make a recommendation for tandem vs. single autologous SCT. (**No Recommendation, Highest Level of Evidence 2-**)
5. Allogeneic SCT with a matched related donor is recommended if available. A matched unrelated donor allogeneic SCT using reduced intensity conditioning may provide equivalent outcomes. (**Grade of Recommendation C, Highest Level of Evidence 2+**)
6. There is no evidence of a survival advantage with T-cell depleted grafts from allogeneic donors. (**Grade of Recommendation B, Highest Level of Evidence 1+**)
7. For high risk disease, allogeneic PBSCT is recommended over BMT. For low risk disease, allogeneic PBSCT and BMT have equivalent outcomes. (**Grade of Recommendation C, Highest Level of Evidence 2++**)

8. There are insufficient data to make a recommendation for PBSCT vs. BMT in matched unrelated donor SCT. (**No Recommendation, Highest Level of Evidence 2++**)

Therapy Regimens

1. There is no evidence of a survival advantage with any one high dose therapy regimen in autologous SCT. (**Grade of Recommendation C, Highest Level of Evidence 2+**)
2. There is no significant survival advantage with any one myeloablative conditioning regimen in allogeneic SCT. Studies of late effects may change this recommendation. (**Grade of Recommendation B, Highest Level of Evidence 1+**)
3. Fractionated rather than a single dose total body irradiation (TBI) conditioning regimen is recommended in allogeneic SCT. (**Grade of Recommendation B, Highest Level of Evidence 1+**)
4. There are insufficient data to make a recommendation for RIC for allogeneic SCT. The use of RIC is dependent on patient characteristics. (**No Recommendation, Highest Level of Evidence 2++**)

Note: See also the National Guideline Clearinghouse (NGC) summary of the American Society for Blood and Marrow Transplantation (ASBMT) guideline on the role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in children.

Definitions:

Levels of Evidence	
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1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
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3	Nonanalytic studies (e.g., case reports, case series)
4	Expert opinion

Â

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults

POTENTIAL HARMS

- Toxicity of treatment, including treatment-related mortality
- Long term complications of chemotherapy or cytotoxic therapy

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The strengths of this systematic evidence-based review are the details conveyed in the text about each study´s design, the presentation of outcomes in summary tables for each major section, and the treatment recommendations made by the adult acute myelogenous leukemia (AML)

expert panel. A limitation of this systematic evidence-based review is the inclusion of only published data, specifically peer-reviewed articles published since 1990. Unpublished data can represent "negative" findings that could lead to publication bias; however, the inclusion of high-quality, peer-reviewed publicly available data was of paramount importance. Also excluded were data published in abstract form because abstracts do not adequately convey the full details of the study design or patient characteristics to meet evidence-based criteria for inclusion in systematic reviews, nor for making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial.

- A limitation of the studies included in this review is the inability to provide level "1" evidence for allo-hematopoietic stem cell transplantation (HSCT) trials because of the low rate of patients allocated to the allo-HSCT arm who would actually receive the assigned treatment (approximately 35% of patients have a matched-related donor). Therefore, trials that biologically allocate patients to allo-HSCT based on donor availability have level "2" as their highest evidence grade.
- Other study-specific limitations that affect the quality of this systematic evidence-based review include the variability in reporting patient characteristics pre-HSCT, changing treatment modalities over time, and the paucity of randomized controlled trial (RCT) data on sufficiently large patient populations. The success of most therapies is affected by cytogenetic risk, which is either not reported, not collected, or missing on too many patients. Chemotherapy regimens, human leukocyte antigen (HLA) typing techniques, pre-HSCT treatment regimens, stem cell sources, and post-HSCT supportive care have changed considerably over the 17 years of trials included in this review. The clinical research process is lengthy, making the data from many of these studies outmoded at the time of publication. RCT data were lacking in many areas of this review, leading to several treatment recommendations based on small prospective studies and/or large retrospective registry reports.
- To address some of these limitations, the authors recommend methodology standardization, including use of consistent study designs, endpoint definitions, and reporting of study results. Multicenter randomized phase III comparative trials with large enrollments and high statistical power are required to advance the field more constructively than single institution phase II trials with 1 treatment arm, or retrospective multicenter or registry studies. Much of today´s therapies for cancer result from the randomized clinical trial process. It is currently estimated that <5% of adult cancer patients who are eligible to participate in clinical trials actually enroll in a trial. The authors acknowledge the importance of removing barriers to participation in clinical trials, which may include patients´ reluctance to be randomized, lack of patient access to clinical trials (e.g., geographic, transportation, cultural), financial restraints (no or incomplete insurance coverage for trial expenses), stringent trial eligibility criteria, and reluctance of community physicians to refer patients for clinical trial participation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Feb

GUIDELINE DEVELOPER(S)

American Society for Blood and Marrow Transplantation - Professional Association

SOURCE(S) OF FUNDING

National Marrow Donor Program

GUIDELINE COMMITTEE

Adult Acute Myeloid Leukemia (AML)Â Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Society for Blood and Marrow Transplantation (ASBMT) documents, along with links to individual position statements and evidence-based reviews are available in Portable Document Format (PDF) from the ASBMT Website.

Print copies: Available from Theresa Hahn, PhD, Roswell Park Cancer Institute, Medicine, Elm and Carlton Sts, Buffalo, NY 14263 (e-mail: theresa.hahn@roswellpark.org).

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on November 17, 2009. The information was verified by the developer on December 16, 2009.

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